UNITED STATES DEPARTMENT OF COMMERCE
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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/983,367	11/30/92	SASISEKHARAN	R MIT5981/6124

EXAMINER
WARE, D

18N2/0706

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ART UNIT	PAPER NUMBER
1808	4

DATE MAILED: 07/06/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☑ Information on How to Effect Drawing Changes, ~~PTO-1474~~ on back of PTO-948.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-17 are pending in the application.
   Of the above, claims 10-17 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-9 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I. Claims 1-9, drawn to a purified heparinase and method of its preparation, classified in Class 435, subclass 183+, 220.

Group II. Claims 10-11 and 12-15, drawn to McAb x-rxn containing heparinase I and III, and further drawn to method of detecting heparinase, classified in Class 435, subclass 7.4.

Group III. Claims 16-17, drawn to enzymatic method of heparin, classified in Class , subclass 435.
18+.

The inventions are distinct, each from the other because of the following reasons:

The inventions of Group I and Group II are distinct from one another in that the product and its method of making of Group I are different from an antibody and a method of detection of enzymes. The method of Groups I and II can be performed using samples derived from the Bacillus group, and Group III requires the use of Heparinum flavobacterium since the sample is derived therefrom and is reacted with antibodies. The methods of purification and detection of Groups I and II can be performed without the use of an antibody, and only with the use of a specific antibody, respectfully. There appears to be two way distinctness between each of the separate products and methods thereof.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter restriction for examination purposes as indicated is proper.

During a telephone conversation with Jamie Greene on May 13, 1993 a provisional election was made with traverse to prosecute the invention of Group I, claim 1-9. Affirmation of this election must be made by applicant in responding to this Office action. Claims 10-17 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

The drawings are objected to because of the reasons set forth on the enclosed PTO-948. Correction is required.

Applicant is required to submit a proposed drawing correction in response to this Office action. However, correction of the noted defect can be deferred until the application is allowed by the examiner.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure.

Since the microorganism is essential to the claimed invention it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the microorganism is not so obtainable or available, the requirements of 35 USC & 112, first paragraph may be satisfied by a deposit of the microorganism. The specification does not disclose a repeatable process to obtain the microorganism and it is not apparent if the microorganism is readily available to the public. The specification must contain the date that the microorganism was deposited, the name of the microorganism and the address of where the microorganism was deposited. It is noted that the applicant(s) have deposited the organism but there is no indication in the specification as to public availability.

If the deposit <u>is</u> made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and

registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in MPEP 608.01 (p) C. applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and,

(d) the deposit will be replaced if it should ever become inviable.

Claims 1-9 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claim 4 is rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the

specific stabilizing protein. It appears that the claims are too broad for the use of all proteins with heparinase III which would work well as stabilizers.

Claims 1-9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2 are vague and indefinite for the recitation of the language "free of other lyase activity" since it is not clearly defined in the claims what "other" lyase activity the purified enzymes are "free of". The language does not define a purified enzyme such that one of skill can determine what other enzymatic activities are pure or not pure.

Claim 6 is vague and indefinite in that it is not clear if the cells are derived from a biologically pure culture. Also it appears that the "lysing" step of the claimed method is not clear in that the method does not describe how the lysing step is performed.

Claims 1-2 and 6 are vague and confusing in that it appears that there are two different microbes used. One called is called "Heparinum favobacterium" and the other is called "H. flavobacterium". Perhaps this is an error, however, the claims appear to be confusing in that claim 6 is a method of making a purified heparinase using a different microbe than the purified heparinase of claims 1-3. Although the claims are directed to

related subject matter it is unclear that the purified heparinases of claim 1-3 are made by the method of claims 6-9.

Claims 1-9 are rejected under 35 U.S.C. § 101 because the claimed invention appears to be directed to non-statutory subject matter in that it is unclear if Heparinum flavobacterium is isolated from nature. The use of the language "biologically pure" inserted before the name of the microbe would be helpful in overcoming this rejection.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-9 are rejected under 35 U.S.C. § 103 as being unpatentable over Zimmerman et al. and Kikuchi et al..

The claims are drawn to purified heparinase II and III which are isolated from Heparinum favobacterium and free of other lyase activity. Furthermore, a method for purifying heparinase I, II and III from Heparinum flavobacterium is claimed.

Zimmerman et al. teach the purification of heparinase using Flavobacterium heparinum microorganism (abstract). Also described is lysing cells, removal of cell debri from the cell lysate, absorption of heparinase to hydroxyapatite using a salt gradient in order to enrich the enzyme (col. 1, lines 35-50). Further described is that an improved purification process is enhanced while combining the hydroxylapatite chromatography with gel filtration and other chromatographic techniques (col. 1, lines 55-60), i.e. FPLC, col. 6, line 62.

Kikuchi et al. teach purification of glycoaminoglycans using chromatographic techniques (abstract). The disruption of Flavobacterium cells to obtain a crude enzyme extract in order to obtain a starting material. Then the extract is applied to a hydroxyapatite column and using an increasing salt concentration gradient which separates the desired enzymes in order to purify (col. 5, example 1) and obtain heparinase. Further the enzyme activity is measured and assayed to test for the purity or presence of other enzyme activities (col. 6, lines 1-5).

The claimed subject matter differs from the disclosure of Zimmerman et al. in that heparinases I, II, and III are purified in place of heparinase as taught by Zimmerman et al.. The significant teachings of Kikuchi et al. do not add the I, II, or III heparinase, however, the reference further supports the wide use of chromatographic techniques to purify heparinase.

It would have been obvious to one of ordinary skill in the art at the time of applicants' invention to utilize the methods disclosed by the above cited references in order to purify heparinases I, II, and III as claimed herein. Further, the use of proteins as stabilizers and protamine as a precipitating agent is well known in the art and the use of such components in applicants' claimed method would have been obvious as well.

Furthermore, one of skill would have expected for heparinases I, II, and III to be purified by the same methods employed for the purification of heparinase (note cited references). Especially since the referenced methods and the claimed method are so similar in their modes of operation.

Thus, all claims fail to be patentably distinguishable over the state of the art discussed above and cited on the enclosed PTO-892 and/or PTO-1449. Therefore, the claims are properly rejected.

The remaining references listed on the enclosed PTO-892 and/or PTO-1449 are cited to further show the state of the art.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah K. Ware whose telephone number is (703) 308-6037.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Deborah K. Ware

June 26, 1993

DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 182